## REMARKS

Currently, claims 1-6, 29-56 and 60-68 are pending in the present application. Claims 29-56 and 60-62 have been withdrawn. Claims 7-28 and 57-59 have been cancelled. Claims 1, 63, 64 and 67 have been amended herein. Claims 1, 63 and 64 have been amended to recite ortho-, meta- and para-hydroxylated atorvastatin metabolites. Claim 67 has been amended merely to correct a typographical error. The amendment to claims 1, 63 and 64 is supported by disclosure at page 3, paragraph 7 of the specification. No new matter has been added as a result of the above amendments.

**Claim Rejections**

**35 USC § 112, first paragraph**

Claims 1-6, 57-59 and 63-68 were rejected under 35 USC 112, first paragraph for lack of written description. According to the Examiner, the specification does not provide adequate support for generic claims encompassing any atorvastatins hydroxylated in any positions in atorvastatin and any atorvastatin metabolites. The Examiner asserts that the specification merely discloses a single specific compound, and that ordinary artisans could not predict the operability of any other species of hydroxylated atorvastatin metabolite. Applicant traverses.

Claims 1, 63 and 64 have been amended to recite the hydroxylation positions of the atorvastatin metabolites. Specifically the claims recite ortho-, meta- and para-hydroxylated metabolites of atorvastatin. These metabolites are disclosed in the instant specification, and the chemical structures of these hydroxylated metabolites and their methods of preparation are taught in U.S. Pat. No. 5,385,929 ("the '929 patent"). *See* Specification at page 3, paragraph 7. Moreover, one of ordinary skill in the art would understand the meaning of the terms ortho-, meta- and para-.

In light of the amendments made herein, Applicant contends that the claims are adequately supported by the specification as filed, thereby satisfying the written description requirement. Thus, Applicant respectfully requests reconsideration and withdrawal of this rejection.

In addition, claims 1-6, 57-59 and 63-68 were rejected under 35 USC 112, first paragraph for lack of written description. According to the Examiner, the specification does not recite "a substantially pure form", and therefore the claims, as previously amended, contain new matter. Applicant respectfully disagrees.

The present specification discloses that the hydroxylated metabolites of atorvastatin and their methods of preparation are shown in U.S. Pat. No. 5,385,929. *See*, Specification at page 3, paragraph 7. Such a reference to U.S. Pat. No. 5,385,929 implies that the entire contents of the '929 patent are incorporated into the instant specification. "Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed. Replacing the identified material incorporated by reference with the actual text is not new matter." MPEP 2163.07(b). The '929 patent discloses the hydroxylated metabolites of atorvastatin in a substantially pure form. *See e.g.*, U.S. Pat. No. 5,385,929 at claims 3-10.

Consequently, Applicant asserts that the limitation "a substantially pure form" can be imported from the '929 patent into the present specification, and does not constitute new matter. Thus, this rejection should be withdrawn.

**35 USC § 102**

Claims 1-6, 57-59 and 63-67 were rejected under 35 USC 102(e) as being anticipated by Buch (U.S. Pat. No. 6,455,574). The Examiner contends that "Buch discloses a composition comprising the combination of an effective amount of amlodipine or its pharmaceutically acceptable salt, amlodipine besylate, and an effective amount of atorvastatin calcium or its pharmaceutically acceptable salt (which reads on 'hydroxylated atorvastatin metabolite', for treating the same diseases as instantly claimed ... ." The Examiner cites Schering Corp. v. Geneva Pharmaceuticals, Inc., 68 USPQ2d 1760 (CAFC 2003) where the court ruled that the metabolite of loratadine, DCL, was inherently anticipated by loratadine (Claritin™) because it was necessarily produced in the patient's body upon ingestion of Claritin™. Employing analogous reasoning, the

Examiner argued that atorvastatin disclosed by the Pfizer News anticipates hydroxylated atorvastatin metabolite. Thus, the Examiner concluded that "the disclosure of Buch anticipates the instant claimed composition". Applicant disagrees.

The Court in Schering, in particular section II last paragraph, states "[a] skilled patent drafter, however, might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form, as in Kratz and Bergstrom, or as a pharmaceutical composition ... ." Applicant has previously amended independent claims 1, 63 and 64 to include the limitation "a substantially pure form of" hydroxylated atorvastatin metabolite. As argued above, support for this limitation can be found in the present specification, for example, on page 3, paragraph 7, which specifically discloses that the hydroxylated atorvastatin metabolites and their methods of preparation are shown in U.S. Patent No. 5,385,929.

An isolated, substantially pure metabolite is not the same as intermediates produced *in vivo* upon ingestion of a parent compound. Therefore, atorvastatin calcium disclosed in Buch does not anticipate the hydroxylated atorvastatin metabolites that comprise one element of the presently claimed compositions.

Moreover, the claims require that the composition synergistically inhibit lipid peroxidation or synergistically achieve an antioxidant effect. Buch does not teach a synergistic combination of amlodipine and metabolites of atorvastatin. Therefore, Buch does not anticipate the invention as currently claimed.

Since Buch does not teach each and every element of the claimed composition, the composition as presently claimed is novel over Buch. Thus, the present rejection should be withdrawn.

**35 USC § 112, first paragraph**

Claim 68 was rejected under 35 USC 112, first paragraph for lack of enablement. The Examiner maintains that while the specification enables the combination of amlodipine and atorvastatin metabolite further comprising the particular and specific antioxidant, it does not enable any substances or compounds represented by "an endogenous and/or exogenous antioxidant". The Examiner contends that the limitation "endogenous and/or exogenous antioxidant" is merely functional. In response to

Applicant's arguments filed February 7, 2005, the Examiner argues that one of skill in the art would be required to perform an exhaustive search for the embodiments of any known and unknown antioxidants encompassed by the instant claims. Furthermore, he argues that administering the combination of amlodipine and atorvastatin metabolite and any substance or compound represented by "an endogenous and/or exogenous antioxidant" would yield highly unpredictable therapeutic effects, side effects, and possible toxicity. Therefore, the Examiner concludes that the specification fails to provide information that would allow the skilled artisan to fully practice the invention without undue experimentation. Applicant disagrees.

Functional language describes the invention's effect on other things but fails to describe the invention itself. The effect of an antioxidant is to inhibit the oxidation of another compound or substance. For example, the instant specification discloses that the claimed invention synergistically prevents lipid peroxidation in human low-density lipoproteins (LDL) and lipid membranes. *See e.g.*, Specification at page 4, paragraph 13. In contrast, the recitation, "an endogenous and/or exogenous antioxidant" is an element of the claimed invention, *i.e.* it describes an ingredient of the pharmaceutical composition. The terms endogenous and exogenous define the source of the antioxidant. Therefore, the limitation, "an endogenous and/or exogenous antioxidant", is not merely functional language, but rather descriptive language.

The Examiner further articulates the concern that it is highly unpredictable in regard to combining the antioxidants with amlodipine and atorvastatin. However, it is well known and appreciated in the art that antioxidants, *e.g.*, vitamins A, C and E, can be taken without serious side effects. In fact, the claim construction requires an "effective amount" of atorvastatin and amlodipine - consistent with the claim language, it is understood that the additional antioxidant ingredient would be an effective amount. Moreover, claim 68 was previously amended to recite an effective amount of antioxidant. Antioxidants, such as those mentioned above, have known toxicity profiles. Nothing in the prior art suggests that these antioxidants used in combination with atorvastatin and amlodipine increase or exacerbate known toxicity.

In conclusion, both endogenous and exogenous antioxidants were well known to those skilled in the art at the time the current application was filed. The

pharmacokinetics and dynamics of these antioxidants are well understood and suggest that an effective, physiological amount will not result in prohibitive toxicity. The claimed invention indicates that these antioxidants will complement the atorvastatin/amlodipine combination. The prior art provides for sufficient detail on the pharmacology of the antioxidants as of the filing of this application. Therefore, the present specification is fully enabled with respect to 35 USC 112, first paragraph. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

**35 USC § 112, second paragraph**

Claims 2-3 and 58-59 were rejected under 35 USC 112, second paragraph for lack of enablement. The Examiner states that "the recitation, 'derivative of amlodipine' renders claims 2-3 and 58-59 indefinite." The Examiner continues, "the recitation, 'derivative of amlodipine' is not clearly defined in the specification. Hence, one of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patent protection ...". Applicant disagrees.

The term "derivative" is well understood by those skilled in the art. Moreover, it is well established that plain meaning is to be applied to any term within a claim. Derivative is defined in Webster's Universal College Dictionary, 1991, Random House, as "3. a chemical substance or compound obtained or regarded as derived from another substance or compound." The Dictionary of Scientific and technical Terms, 3rd ed., 1984, McGraw-Hill, defines derivative as " a substance that is made from another substance." It is not a terribly difficult concept to understand what derivative means. A derivative is a compound that is derived from a parent compound, *e.g.*, amlodipine. Moreover, claim 2 requires that the derivative of amlodipine be an effective derivative. Therefore, the derivative must act similarly to amlodipine, *i.e.*, an effective derivative of amlodipine in combination with a hydroxylated atorvastatin metabolite, which synergistically inhibit lipid peroxidation. Furthermore, claim 3 provides for a specific example of a derivative of amlodipine, a salt derivative of amlodipine.

In conclusion, Applicant contends that the term "derivative" is not indefinite and that in fact, it is well understood by the skilled artisan. Hence, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

**35 USC § 102**

Claims 1-6, 57-59 and 63-67 were rejected under 35 USC 102(b) as being anticipated by the Pfizer News, May 20, 1997. The Examiner maintains that "Pfizer News discloses the combination of Norvasc also known as amlodipine besylate . . . and Lipitor also known as atorvastatin calcium in their effective amounts for treating cardiovascular diseases .... Hydroxylated atorvastatin metabolite claimed herein is a metabolite of atorvastatin, which was necessarily produced in the patient's body upon ingestion of atorvastatin .... Thus, atorvastatin disclosed by the Pfizer News would anticipate hydroxylated atorvastatin metabolite." In the proffered argument, the Examiner cites Schering Corp. v. Geneva Pharmaceuticals, Inc., 68 USPQ2d 1760 (CAFC 2003). Applicant disagrees.

As argued above with regard to whether claims 1-6, 57-59 and 63-67 are anticipated by Buch (U.S. Pat. No. 6,455,574), The Court in Schering, in particular section II last paragraph, states "[a] skilled patent drafter, however, might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form, as in Kratz and Bergstrom, or as a pharmaceutical composition ...." Applicant has previously amended independent claims 1, 63 and 64 to include the limitation "a substantially pure form of" hydroxylated atorvastatin metabolite. As argued above, support for this limitation can be found in the present specification, for example, on page 3, paragraph 7, which specifically discloses that the hydroxylated atorvastatin metabolites and their methods of preparation are shown in U.S. Patent No. 5,385,929.

An isolated, substantially pure metabolite is not the same as intermediates produced *in vivo* upon ingestion of a parent compound. Therefore, atorvastatin calcium disclosed in Pfizer News does not anticipate the hydroxylated atorvastatin metabolites that comprise one element of the presently claimed compositions.

Moreover, the claims require that the composition synergistically inhibit lipid peroxidation or synergistically achieve an antioxidant effect. Pfizer News does not teach a synergistic combination of amlodipine and metabolites of atorvastatin. Therefore, Pfizer News does not anticipate the invention as currently claimed.

Since Pfizer News does not teach each and every element of the claimed composition, the composition as presently claimed is novel over Pfizer News. Thus, the present rejection should be withdrawn.

**35 USC § 103**

Claim 68 was rejected under 35 USC 103(a) as being unpatentable over Buch (U.S. Pat. No. 6,455,574) or the Pfizer News, May 20, 1997 in view of Gilligan *et al.* (J. Amer College Card., 1994, 24(7), 1611-7. The Examiner refers back to argument put forth for the 102 rejection with respect to Buch or Pfizer News. However, the Examiner adroitly points out that the "News does not expressly disclose the combination therein further comprising an antioxidant." The Examiner continues and states that "Gilligan *et al.* teaches that antioxidants such as Vitamin A, C, and E are known to be used in the treatment of hypercholesterolemia in humans." The Examiner concludes by stating "It would have been obvious to a person of ordinary skill in the art at the time the invention was made to further employ antioxidants such as Vitamin A, C, and E in the composition for treating ... ." Applicant disagrees.

In order to establish a prima facie case of obviousness, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references) must teach or suggest all of the claim limitations." M.P.E.P. §2143, *see also, In re* Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

There is no teaching or suggestion in the art cited to combine the composition of amlodipine/atorvastatin metabolite with one or more antioxidants, including any vitamin. Neither alone or in combination do the cited art teach or disclose the synergistic effect of using amlodipine and atorvastatin metabolite in combination further in combination with

an antioxidant. Without such teaching or suggestion, there can be no prima facie case of obviousness.

The Examiner asserts that if one skilled in the art would reasonably expect that "adding an antioxidant ... to the combination of amlodipine and atorvastatin would improve the anti-lipidemia effect of the combination." Importantly, claim 63 requires a "synergistic" effect which is clearly distinct from a mere "improvement". Further, there is no suggestion, data or alike which suggests that combining Buch or Pfizer News with Gilligan would result in even an improvement in any therapeutic effect.

Moreover, both Buch and Pfizer News fail to teach the atorvastatin metabolite, hence the all elements requirement is not met by this combination of cited art. (See above for a discussion of metabolite vs. parent compound.)

In conclusion, Applicant contends that the composition as defined by claim 68 is nonobvious over the combination of the teachings of Buch or Pfizer News and Gilligan *et al.* Therefore, Applicant respectfully requests reconsideration and withdrawal of the present rejection.

**Double Patenting**

Claims 1-6, 57-59 and 63-67 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 118-147 of copending Application No. 10/214,058 or claims 84-86 and 118-192 of copending Application No. 10/637,781. Applicant respectfully disagrees.

Applicant asserts that the pending claims are patently distinct from both US Application No. 10/214,058 and 10/637,781. Applicant's claimed invention recites a substantially pure hydroxylated atorvastatin metabolite while the two cited applications do not. Hence, Applicant contends that his claimed invention is patentably distinct from both of the cited applications, and this rejection should be withdrawn.

In conclusion, in view of the above amendments and remarks, Applicant respectfully requests the Examiner find the pending claims in condition of allowance and, therefore, issue a Notice of Allowance.

A petition for a one-month extension of time along with the appropriate fee is filed herewith. The Commissioner is authorized to charge any underpayment of fees to or credit any overpayment of fees to Deposit Account No. 03-2410.

The Examiner is invited to call the undersigned attorney at (617) 854-4069 should he determine that a telephonic interview would expedite prosecution of this case.

Respectfully submitted,

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